

**DAY 10**

	Vehicle			ACV			TCP		
	% T (n = 13)	% R (n = 7)	Ave Copy #	% T (n = 8)	% R (n = 8)	Ave Copy #	% T (n = 12)	% R (n = 11)	Ave Copy #
Lung	92	86	48218	0	0	0	0	0	0
Spleen	77	57	359	13	13	114	17	8	112
Kidney	54	14	186	0	0	0	0	0	0
Cerebral Cortex	92	86	7553	25	25	92	42	36	678
Olfactory Lobes	77	57	2040	25	25	310	25	18	338
Cerebellum	85	71	14681	63	63	1353	42	36	1188

### Scoring Criteria for Ocular Disease in the Rabbit Eye Model

	0 No manifestations	+1 Slight manifestations	+2 Moderate manifestations	+3 Severe manifestations
Corneal Epithelium	Normal	5-25% loss	26-50% loss	> 50% loss
Corneal Stroma	No coloration	Slight thickening of stromal area	Coloration with thickening & scarring	Coloration of > 90% stromal area, thickening & open sores
Scleral Inflammation/ Injection	No redness or prominent vessels	Red tinge with visible vessels	Prominent vessels & localized chemosis	Hyperemia with indistinguishable vessels
Ocular Neovascularization	No visible vessels	Developing vessel network with < 25% surface area affected	Vessel network with 26-75% surface area affected	Prominent vessel network with > 75% surface vascularized

**A**

**Scoring HSV Primary Disease & Recurrence  
in the Guinea Pig Model**

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- 0.0      No disease**
- 0.5      Redness, no visible vesicles**
- 1.0      1-3 small individual vesicles**
- 1.5      > 3 individual vesicles**
- 2.0      1-3 large lesions and several individual vesicles**
- 2.5      > 3 large lesion and several individual vesicles**
- 3.0      1-3 large lesion areas growing into each other**
- 3.5      > 3 large lesion areas growing into each other**
- 4.0      Large ulcers with maceration**

**B**

**Scoring HSV Lesion Recurrence in the Guinea Pig Model**

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- 0.0      No disease**
- 0.5      Non raised lesion**
- 1.0      Old outer lesion**
- 2.0      New outer lesion**
- 3.0      Internal lesion**

Figure	Model	Virus	Infection	Innoculum	Treatment	Inhibitor	Control	n/Group	Treatment Period
			Mode		Mode		Treatment		DPI
<b>Figure 2</b>									
B	Mouse	HSV-1(F)	Ocular	$2 \times 10^5$	Topical	TCP 5 mM	ACV 5 mM	10	+1 to +13
C	Mouse	HSV-1(F)	Ocular	$2 \times 10^5$	IP	TCP 5-10 mg/kg	ACV 100 mg/kg	10	+1 to +10
D-F/S1	Mouse	HSV-2(MS)	Intranasal	$LD_{50}$	Oral	TCP 15 mg/kg	ACV 100 mg/kg	8-16	-7 to +10
G-H	Mouse	HSV-2(MS)	Intranasal	$LD_{90}$	Oral	TCP 2-6 mg/kg	ACV 100 mg/kg	15	-7 to +7
I	Mouse	HSV-2(MS)	Intranasal	$LD_{90}$	Time Release Pellet	TCP 3.5-14 mg/kg	ACV 100 mg/kg	15	-7 to +14
J	Mouse	HSV-2(MS)	Intranasal	$LD_{90}$	Oral	TCP 1.5-15 mg/kg	ACV 6-20 mg/kg	15	-7 to +1
<b>Figure 3</b>									
A-G	Rabbit	HSV-1(17syn+)	Ocular	$2.5 \times 10^5$	Oral	TCP 12 mg/kg	VCV 30 mg/kg	5 Rabbits (10 Eyes)	-2 to +21
<b>Figure 4</b>									
A-B	Rabbit	HSV-1(17syn+)	Ocular	$3 \times 10^5$	Oral	TCP 12 mg/kg	VCV 250 mg/kg	5 Rabbits (10 Eyes)	+28 to +53
C-D/G	Rabbit	HSV-1(17syn+)	Ocular	$3 \times 10^5$	Time Release Pellet	TCP 8.4 mg/kg	Placebo Pellet	5 Rabbits (10 Eyes)	+48 to +68
E-F/H	Rabbit	HSV-1(17syn+)	Ocular	$3 \times 10^5$	Time Release Patch	EMSAM (SEL) 5.5 mg/kg	Vehicle Patch	5 Rabbits (9 Eyes)	+17 to +47
<b>Figure 5</b>									
A	Rabbit	HSV-1(17syn+)	Ocular	$2 \times 10^5$	Time Release Pellet	TCP 8.4 mg/kg	Placebo Pellet	5 Rabbits (5 ganglia)	+45 to +67
B	Rabbit	HSV-1(17syn+)	Ocular	$3 \times 10^5$	Time Release Patch	EMSAM (SEL) 5.5 mg/kg	Vehicle Patch	5 Rabbits (5 ganglia)	+17 to +47
C-E	Mouse	HSV-1(F)	Ocular	$2 \times 10^5$	Time Release Pellet	TCP 1.2-12 mg/kg/day	Placebo Pellet	15 mice (30 ganglia)	+45 to +66
<b>Figure 6</b>									
A-F/K	Guinea Pig	HSV-2(MS)	Intravaginal	$1 \times 10^6$	Oral	TCP 15 mg/kg	ACV ad libitum	15	15-35
G-J/L	Guinea Pig	HSV-2(MS)	Intravaginal	$2 \times 10^5$	IP	TCP 5 mg/kg	ACV 6 mg/kg	5	22-43

Figure	Description	Test	p	p2	n	Significance
<b>Figure 2</b>						
B	TG viral loads	Anova-Dunnett's post hoc	0.0011		Veh=15; TCP5=8; TCP10=8; ACV=10	TCP 5 and 10 mg/kg, ACV 50 mg/kg are significant compared to Vehicle
D	TG viral loads	Anova-Dunnett's post hoc				
	Day 5		0.0037		8	ACV and TCP are significant compared to Vehicle
	Day 10		0.0339		8	ACV and TCP are significant compared to Vehicle
G	TG viral loads	Anova-Dunnett's post hoc				
	Day 3		0.0542		6	TCP is significant compared to Vehicle
	Day 5		0.0018		6	ACV and TCP are significant compared to Vehicle
	Day 7		0.0311		6	ACV is significant compared to Vehicle
H	TG viral loads	Anova-Dunnett's post hoc				
	Day 3		<0.0001		7	ACV and TCP (7 mg/kg) are significant compared to Vehicle
	Day 7		<0.0001		7	ACV and TCP (14 mg/kg) are significant compared to Vehicle
<b>Figure 3</b>						
A	Eye swabs yields	Holm Sidak Multiple t tests	Veh vs TCP	Veh vs VCV	6 animals-12 eyes per group	
	Day 3		0.1173	0.3503		
	Day 4		<0.0001	<0.0001		
	Day 5		<0.0001	<0.0001		
	Day 6		<0.0001	<0.0001		
	Day 7		0.1578	0.2443		
	Day 8		0.8113	0.884		
G	Cumulative disease scores	Linear Regression-Slope Analyses	0.0029			<0.29% random chance; differences between slopes-extremely significant
<b>Figure 4</b>						
B	Eye swabs HSV-1 DNA	Anova-Dunnett's post hoc	<0.0001		Vehicle=77; VCV=36; TCP=7	ACV and TCP are significant compared to Vehicle (copy # of positives)
D	Eye swabs per rabbit	unpaired 2-tailed t-test	0.0028		34	
F	Eye swabs per eye	unpaired 2-tailed t-test	<0.0001		28 per eye; 9 eyes per group	
G	Viral load ganglia	unpaired 2-tailed t-test	0.9397		5	No significant difference in viral loads
H	Viral load ganglia	unpaired 2-tailed t-test	0.9706		5	No significant difference in viral loads
<b>Figure 6</b>						
A	Cumulative average lesion score	Linear Regression Analyses	<0.0001		27	<0.01% random chance; differences between slopes-extremely significant
B	Lesion score per day	Anova-Dunnett's post hoc	0.0008		27	ACV and TCP are significant compared to Vehicle
C	Cumulative lesion score per gp	Anova-Dunnett's post hoc	0.0348		11	ACV and TCP are significant compared to Vehicle
E	Vaginal Swabs Viral DNA	Anova-Dunnett's post hoc	0.0321		Vehicle=11; ACV=11; TCP=12	TCP is significant compared to Vehicle; ACV is not significant
F	DRG and spinal cord loads	Anova-Dunnett's post hoc	0.5826-DRG	0.5588-SC	Vehicle=11; ACV=10; TCP=12	No significant differences in viral loads
G	Cumulative recurrences	Linear Regression Analyses	<0.0001		22	<0.01% random chance; differences between slopes-extremely significant
J	DRG viral loads	Anova-Dunnett's post hoc	0.4585		5	No significant difference in viral loads

## PRIMERS

<b>TARGET</b>	<b>SEQUENCE</b>
<i>qPCR-Viral Genomic Loads</i>	
GAPDH-Mouse	CTGACGTGCCGCCTGGAGAAA CCCGGCATCGAAGGTGGAAGAGT
GAPDH-Rabbit	ATTGTGGAGGGGCTCATGAC GTGGAGGCAGGGATGATGTT
GAPDH-Guinea Pig	TTGAGCTGGATGATGCTGAGTGGAA TCCTGGCTTGGGAAGTTCTGTTCT
HSV2-gD	TCAGCGAGGATAACCTGGGA GGGAGAGCGTACTTGCAGGA
HSV1-gD	GTCAGCGAGGATAACCTGGGG GGGAGGGCGTACTTACAGGAGC
HSV1/2 UL30	AGAGGGACATCCAGGACTTTGT CAGGCCTTGGTGTAC
HSV2-gG	CGGAGACATTGAGTACCAAGATC GCCCACCTCTACCCACAACA
HSV2-gG FAM/TAM probe	FAM-ACCCACGTGCAGCTCGCCG-TAM
HSV2-UL30	ACCGCCGAACTGAGCAGAC TGAGCTTGTAAATACACCGTCAGGT
HSV2-UL30 BHQ probe	CGCGTACACCAACAAGCGCCTG
<i>qPCR- ChIP</i>	
HSV1 ICP0	CATTGGGGAATCGTCACTG TTCTGTGGTATGCGGAGAG
HSV1 ICP4	GCCCCTGGACTATATGAGC GCGTCTGACGGTCTGTCTCT
HSV2 ICP0	GGCGCGCATGCTAATG GGCGGCATTACGATTCC
GAPDH promoter-Rabbit	TATAAAATTGAGGCTGCGGGTT CTAGCACTGCACGAGAAGAAG
GAPDH promoter-Guinea Pig	CCCGCCTAACTGCTATAAAGG TGCACGGGAAGAAGGAATAC

## ANTIBODIES

Control IgG	Millipore 12-370 & Millipore NG1893918
Histone H3-lysine9-me3	Abcam ab8898
Histone H3	Abcam ab1791
Histone H3-lysine27-me3	Active Motif 39156